

REMARKS

With entry of the amendments, claims 1-3 and 5-14 are pending in the application. In the Advisory Action mailed September 23, 2002, the Examiner withdrew the following rejections: rejection of claims 1 and 15 under 35 U.S.C. 112, first paragraph; rejection of claims 12 and 15 under 35 U.S.C. 102 over Barnes *et al.*, and the rejection of claims 12, 14, and 15 under 35 U.S.C. 102(e) over Stice *et al.* The Examiner has maintained the rejection of claims 12, 14 and 15 under 35 U.S.C. 102(b) over Gurdon, and the rejection of claims 1-15 under 35 U.S.C. 103(a) as being unpatentable over Prather *et al.*, Gurdon, Campbell *et al.*, Telford *et al.*, Dominko *et al.*, in further view of Stice *et al.*

The outstanding rejections were discussed in an October 16, 2002 telephonic interview with Examiner Woitach, Dr. Neal First, and Attorney Jill Fahrlander. The Examiner indicated that he would favorably consider amendments to the claims to include embryos that have undergone maternal to embryonic transition. Applicants express their gratitude to Examiner Woitach for the courtesy of his time and for his helpful suggestions. This amendment is accompanied by a declaration under 37 C.F.R. 1.132 of Dr. Neal First ('the First declaration').

Applicants have amended claim 1 to reflect that donor cells used in methods according to the present invention are differentiated. Support for differentiated donor cells is found throughout the specification (e.g., p. 7, lines 4-6 and 23-31). Claims 1 and 13 have been amended to clarify that the embryos of the present invention have undergone the maternal to embryonic transition. Support for maternal to embryonic transition can be found at p. 13, line 27-p. 14, line 2). Claim 5, which depended from cancelled claim 4, has been amended to depend from claim 1. The amendment introduces no new matter and places the claims in better condition for allowance or consideration on appeal.

In view of the amendments above and the arguments below, Applicants respectfully request reconsideration on the merits of the application and allowance of the claims.

Rejections under 35 U.S.C. 102(b)

Claims 12, 14, and 15 stand rejected as being anticipated by Gurdon (J. Cell Sci., 1986). Applicants have cancelled claim 15, thereby obviating this rejection. In the May 9, 2002 Office Action, the Examiner conceded that Gurdon does not specifically teach making embryos that meet the limitation of bovine oocyte. Nevertheless, the Examiner asserted that "Gurdon comtemplates and teaches the general use of trans-species nuclear transfer for the study of development. Further, Gurdon specifically discusses the state of the art for

mammalian nuclear transfer and provides an example wherein the nuclear material was from a mammal. In view of the teachings of the reference as whole, clearly the generation of other trans-species combinations, i.e., nuclear material of one species into a mammalian oocyte for the study of development would be encompassed by the teachings of Gurdon.” (emphasis added).

In the August 8, 2002 response, Applicants argued that a valid rejection under 35 U.S.C. 102(b) requires that the cited art teach every claim limitation. Neither Gurdon nor the work cited therein teach a trans-species nuclear transfer embryo made by inducing the donor cell of a species other than bovine to undergo G₀ arrest, fusing the donor cell to an enucleated bovine oocyte to create a nuclear transfer embryo, and activating the nuclear transfer embryo. Because Gurdon does not teach all of the claim limitations, the rejection under 35 U.S.C. 102(b) over Gurdon is improper.

In the Advisory Action, the Examiner contemplates the possibility of making an embryo according to the present invention. The Examiner stated that “the present claims are directed to a product by process and ‘When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent.’ See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). In the instant case, even if one were to accept the difficulties in repeating a set of experiments previously disclosed in the art, within the breadth of the present claims the ability to combine the nuclear material of one species into the oocyte of a bovine forming a single cell embryo *would have been accomplished* and thus, would anticipate the present claims.” (emphasis added). However, the reference does not disclose the ‘structure’ (i.e., a trans-species nuclear transfer embryo made by inducing the donor cell of a species other than bovine to undergo G₀ arrest, fusing the donor cell to an enucleated bovine oocyte to create a nuclear transfer embryo, and activating the nuclear transfer embryo). Therefore, the rejection under 35 U.S.C. 102(b) based on inherency is improper and should be withdrawn.

However, in the interest of advancing prosecution on the merits, Applicants have amended claims 1 and 13, drawn to methods by which the embryos of claims 12 and 14, respectively, are made. Claims 1 and claim 13 were amended to reflect that trans-species embryos according to the present invention have undergone maternal to embryonic transition.

The First declaration states that “Gurdon teaches that development beyond the maternal to embryonic transition of amphibians reliably occurs if the nuclear transfer donor cell is from a pregastrula or pre-maternal to embryonic stage, but not if the donor cell is at the gastrula stage or has undergone maternal to embryonic transition. The maternal to embryonic

transition of amphibians occurs at the twelfth cell cycle, whereas that of cattle and sheep occurs at the third cell cycle, that of primates and swine occurs at the second cell cycle, and that of rodents in the first cell cycle. Because of the differences in embryo development with respect to mechanisms, genomic imprinting, role of maternal cytoplasm, maternal control of positioning of cells in the embryo, and the like, the amphibian is not considered a good or true developmental model for mammals. The amphibian studies would not be expected to predict the outcome of trans-species nuclear transfer into mammalian oocytes, especially using bovine oocytes. Gurdon cites the work of Brun, who introduced a mammalian donor cell into an amphibian oocyte and produced a cleavage stage embryo, which did not pass the maternal to embryonic transition in development of either the donor or recipient species. Activation of an oocyte that had not received a donor nucleus would also result in a cleavage stage embryo.”

In view of the foregoing, Applicants respectfully request that the rejection of claims 12 and 14 under 35 U.S.C. 102(b) over Gurdon be withdrawn.

Rejection of claims under 35 U.S.C. 103(a)

Claims 1-15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Prather *et al.* (Biology of Reproduction, 1989, Gurdon *et al.* (J. Cell Sci. 1986), Campbell *et al.* (WO 97/07668, March, 1997), Telford *et al.* (Molecular Reproduction and Development, 1990), Dominko *et al.* (Molecular Reproduction and Development, 1997), and Stice *et al.* Applicants have cancelled claims 4 and 15, thereby rendering moot this rejection.

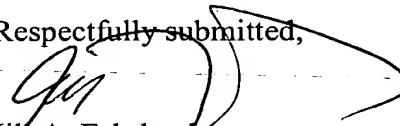
The Examiner found Applicants' arguments that the prior art does not teach trans-species nuclear transfer into an enucleated mammalian recipient oocyte to be unpersuasive and asserted that Gurdon teaches that “trans-species nuclear transfer had been attempted for a wide variety of species of animals, and in view of the teachings of the reference as a whole provides for the use of recipient mammalian oocytes.” Applicants respectfully disagree with the Examiner's characterization of Gurdon. The only hybrid nuclear transplant embryos taught by Gurdon employed amphibian oocytes as recipients. Gurdon did not teach trans-species nuclear transfer into a bovine oocyte. As discussed above, the First declaration points out differences between amphibian and bovine oocytes that render the ability to obtain a trans-species nuclear transfer embryo by trans-species nuclear transfer into an enucleated bovine oocyte unpredictable and non-obvious. This is particularly true when a differentiated cell is used as the donor cell, as required by claims 3, 13, and 14, or when the resulting embryo has undergone the maternal to embryonic transition, as required by claims 1-14.

Applicants have discussed the prior art teachings of the cited references in previous responses, and incorporate herein arguments previously made. Additionally, as pointed out in the First declaration, the Stice *et al.* used undifferentiated embryonic stem cells as bovine donor cells to obtain intraspecies nuclear transfer embryos, whereas the claims 3, 13, and 14 require differentiated cells. Applicants maintain that there is no suggestion in the art to make a trans-species nuclear transfer embryo of any stage of development using a bovine oocyte as the recipient and a donor cell of a species other than bovine, let alone an embryo that has undergone maternal to embryonic transition, and that the art provides no reasonable expectation of success. Therefore, the claims as amended are not *prima facie* obvious. Applicants respectfully request that the rejections under 35 U.S.C. 103(a) be withdrawn.

As the application is now in condition for allowance, Applicants request allowance of the claims. Should the Examiner feel that any other point requires consideration or that the form of the claims can be improved, the Examiner is invited to contact the undersigned at the number listed below.

This response is being timely submitted on November 12, 2002. The statutory period for reply with a 3-month extension of time was set to expire on November 9, 2002, a Saturday. Monday, November 11, 2002, was a Federal holiday. The response is accompanied by a request for a 3-month extension of time and check number 45750 in the amount of \$620.00 to cover the fee required under 37 CFR 1.17(a)(3) for the Extension of Time, and \$160.00 under 37 CFR 1.17(b) for the Notice of Appeal. No other fee is believed due in connection with this submission. Please charge any fee due or credit any overpayment of fees to Deposit Account No. 50-0842.

Respectfully submitted,


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MARKED VERSION OF AMENDED CLAIMS UNDER

37 CFR § 1.121(c)(1)(ii)

All the words, phrases, or numbers added to the claims are underlined, and all words, phrases, or number removed from each such claim are enclosed in brackets ("[]").

1. A method of producing nuclear transfer embryos from donor cells of a species other than bovine and a recipient bovine oocyte comprising:
 - inducing the donor cells to undergo G₀ arrest;
 - fusing said donor cell G₀ arrest to an enucleated recipient bovine oocyte to create a nuclear transfer embryo; [and]
 - activating said nuclear transfer embryo; and
 - culturing the activated embryo to allow the embryo to undergo maternal to embryonic transition.
5. The method of claim 1 [4] wherein said enucleated bovine recipient oocyte is prepared from a bovine oocyte undergoing nuclear maturation within 16 hours of beginning in vitro culture.
13. A method of producing nuclear transfer embryos from a donor cell of one species other than bovine and a bovine recipient oocyte comprising:
 - culturing non-bovine donor cells selected from the group consisting of embryonic derived cells, somatic cells, germ cells, and genetically modified cells in low serum medium so that said donor cells are induced to arrest in the G₀ stage of the cell cycle;
 - selecting a bovine recipient oocyte which has completed nuclear maturation before 16 hours from the beginning of in vitro culture;
 - enucleating said bovine recipient oocyte after 16-32 hours of in vitro culture;
 - placing said donor cell under the zone pellucida of the enucleated oocyte so that said donor cell contacts said enucleated oocyte;
 - fusing said donor cell with said enucleated oocyte by electric pulse at 16-32 hours after the beginning of in vitro culture to create a nuclear transfer embryo; [and]
 - activating said nuclear transfer embryo by sequential incubation with ionomycin and 6-dimethylaminopurine at 16 to 32 hours after beginning of in vitro culture; and
 - culturing the nuclear transfer embryo to allow the embryo to undergo maternal to embryonic transition.